Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Bexarotene 75 mg soft capsules

This is a summary of the risk management plan (RMP) for Bexarotene 75 mg soft capsules. The RMP details important risks of Bexarotene 75 mg soft capsules, how these risks can be minimised, and how more information will be obtained about Bexarotene 75 mg soft capsules risks and uncertainties (missing information).

Bexarotene 75 mg soft capsules summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Bexarotene 75 mg soft capsules should be used.

Important new concerns or changes to the current ones will be included in updates of Bexarotene 75 mg soft capsules RMP.

I. The medicine and what it is used for

Bexarotene 75 mg soft capsules is authorised for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patient refractory to at least one systemic treatment (see SmPC for the full indication). It contains Bexarotene as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bexarotene 75 mg soft capsules, together with measures to minimise such risks and the proposed studies for learning more about Bexarotene 75 mg soft capsules risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of important risks and missing information

Important risks of Bexarotene 75 mg soft capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bexarotene 75 mg soft capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risk(s)	• Hyperlipidaemia

List of Important Risks and Missing Information	
	• Liver function test (LFT) abnormalities • Psychiatric disorders • Thyroid function test abnormalities • Pancreatitis • Leucopenia • Teratogenicity
Important potential risk(s)	• Lens opacities • Hypoglycaemia in patients taking anti-diabetic medications or insulin
Missing information	• None

II.B. Summary of important risk

Important Identified Risk – Hyperlipidaemia	
Evidence for linking the risk to the medicine	A study performed to investigate the effect of bexarotene on lipoprotein levels in 10 patients with metastases of differentiated thyroid carcinoma who received 300 mg/d bexarotene for six weeks revealed that bexarotene increases VLDL-TG and VLDL-C and decreases HDL-C in humans. Furthermore, this study demonstrated that the shift in cholesterol distribution on bexarotene treatment is a consequence of increased endogenous CETP activity. Studies in E3L and E3L.CETP mice provide evidence that increased VLDL-TG production is the cause of the bexarotene-induced hypertriglyceridemia.[11] Study results from an open-label, multicenter, phase 2 and 3 study conducted in 58 patients with biopsy-proven stage IA through IIA cutaneous T-cell lymphoma, to determine the safety and efficacy of oral bexarotene revealed that hyperlipidemia occurred in 46 (79%) of the 58 patients and was considered dose limiting in 25 patients (43%). Rises in lipids were rapid (within 1 to 2 weeks). Twenty patients had peak triglyceride level elevations of higher than 3.4 to 4.5 mmol/L (300 to ≤400 mg/dL); 9 in the range of higher than 4.5 to 5.65 mmol/L (400 to ≤500 mg/dL); and 8 with levels higher than 5.65 mmol/L (500 mg/dL). Hypercholesterolemia was present in 20 (71%) of 28 patients and 10 (67%) of 15 patients beginning therapy at 300 and above 300 mg/m2 per day, respectively. For all dose groups, the median values were 8.1 mmol/L (314 mg/dL) for cholesterol and 5.3 mmol/L (472 mg/dL) for triglyceride levels at 2 to 4 weeks. With anti-lipid therapy, levels remained elevated at 6.9 and 3.7 mmol/L (267 and 333 mg/dL) for cholesterol and triglyceride levels at 12 to 16 weeks, respectively.[12]
Risk factors and risk groups	Several things can contribute to a higher risk of hyperlipidaemia, including: • Having a family history of high cholesterol. • Having hypothyroidism. • Having obesity. • Not eating a nutritious diet. • Drinking too much alcohol.

Important Identified Risk – Hyperlipidaemia	
	• Having diabetes. • Smoking.
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **<u>Additional risk minimisation measures:</u>** None

Important Identified Risk – Liver function test (LFT) abnormalities	
Evidence for linking the risk to the medicine	Study results from an open-label, multicenter, phase 2 and 3 study conducted in 58 patients with biopsy-proven stage IA through IIA cutaneous T-cell lymphoma, to determine the safety and efficacy of oral bexarotene revealed an elevated hepatic function test results (aspartate transaminase or alanine transaminase levels in the range of >2.5 to ≤5.0 × the upper limit of normal) related to bexarotene in 6 (10%) of 58 patients. Transaminase level elevation was dose related with the highest incidence and severity in the 300 mg/m^2 per day initial dose group.[12]
Risk factors and risk groups	• Over-the-counter pain medications, particularly acetaminophen (Tylenol, others) • Certain prescription medications, including statin drugs used to control cholesterol. • Drinking alcohol. • Heart failure. • Hepatitis A, B or C. • Liver disease including primary biliary cholangitis and Nonalcoholic fatty liver disease.
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **<u>Additional risk minimisation measures:</u>** None

Important Identified Risk – Psychiatric disorders	
Evidence for linking the risk to the medicine	Adverse Drug Reactions reported to the World Health Organization include 1095 events related to psychiatric symptoms including 34 suicide attempts/completions and 69 total deaths. Psychiatric symptoms reported include depression, amnesia, anxiety, mood swings, insomnia, and suicide with isotretinoin.[3]
Risk factors and risk groups	• Genetic predisposition • A history of mental illness in a blood relative, such as a parent or sibling

Important Identified Risk – Psychiatric disorders	
	• Stressful life situations • An ongoing (chronic) medical condition, such as diabetes • Brain damage as a result of a serious injury (traumatic brain injury), such as a violent blow to the head • Traumatic experiences • Use of alcohol or recreational drugs • A history of abuse or neglect • A previous mental illness
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **<u>Additional risk minimisation measures:</u>** None

Important Identified Risk – Thyroid function test abnormalities	
Evidence for linking the risk to the medicine	Study results from an open-label, multicenter, phase 2 and 3 study conducted in 58 patients with biopsy-proven stage IA through IIA cutaneous T-cell lymphoma, to determine the safety and efficacy of oral bexarotene revealed that the levels of TSH fell from 1.63 mIU/L (n = 55) median at baseline to 0.36 mIU/L (n = 22) at more than 2 to 4 weeks. Although 2 (4%) of 58 patients had low TSH values at baseline, 28 (48%) and 25 (43%) had abnormally low values during the 2 postbaseline periods. Changes in total thyroxine levels generally corresponded to those of TSH. Twenty-four (41%) of 58 patients were administered levothyroxine at some time during the study based on their symptoms or fall in levothyroxine levels.[12]
Risk factors and risk groups	• Type 1 Diabetes • Lupus • Rheumatoid Arthritis: • Pernicious Anaemia • Primary Adrenal Insufficiency • Sjogren's Syndrome • Turner Syndrome • Iodine deficiency • Non-functioning thyroid gland. • Thyroiditis or swelling of the thyroid gland. • Hashimoto's thyroiditis • Postpartum thyroiditis
Risk minimisation measures	**<u>Routine risk minimisation measures:</u>** SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **<u>Additional risk minimisation measures:</u>**

Important Identified Risk – Thyroid function test abnormalities	
	None

Important Identified Risk – Pancreatitis	
Evidence for linking the risk to the medicine	Acute pancreatitis associated with elevations of fasting serum triglycerides has been reported in clinical studies.[10]
Risk factors and risk groups	• Blockage in the bile duct caused by gallstones. • Heavy alcohol use. • Certain medicines (ACE Inhibitors, Tetracycline, Diuretics, Anticancer therapies etc.). • High triglyceride levels in the blood. • High calcium levels in the blood. • Pancreas cancer. • Injuries from trauma or surgery.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **Additional risk minimisation measures:** None

Important Identified Risk – Leucopenia	
Evidence for linking the risk to the medicine	Leucopenia associated with bexarotene therapy has been reported in clinical studies. The majority of cases resolved after dose reduction or discontinuation of treatment.[10]
Risk factors and risk groups	• Autoimmune conditions, such as rheumatoid arthritis, lupus, and Sjögren's • Cancers, such as Hodgkin lymphoma, leukemia, and myelofibrosis • Infection, such as influenza, HIV, and hepatitis • Inflammatory bowel disease (IBD) • Granulomatosis with polyangiitis, which is a condition that causes the inflammation of the blood vessels • A deficiency in folate, copper, or vitamin B12 • Inherited disorders, such as Chediak-Higashi syndrome or Kostmann syndrome
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL section 2 and 4 Prescription Only Medicine **Additional risk minimisation measures:** None

Important Identified Risk – Teratogenicity	
Evidence for linking the risk to the medicine	Clinical studies have documented teratogenic potential of bexarotene. A study conducted to study teratogenicity and fetal transferability assessment of bexarotene in rats reveled that there were no significant differences in the numbers of implantations and survivors between the normal and bexarotene-administered groups. However, the fetuses in the bexarotene-administered group were smaller than those in the normal group, and their average weight and height were significantly smaller. In addition, it was observed that bexarotene was accumulated in the placenta.[16]
Risk factors and risk groups	• Females of childbearing potential. • Male patients with sexual partners who are pregnant or who are females of childbearing potential.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.6 PL section 2 Prescription Only Medicine **Additional risk minimisation measures:** None

Important Potential Risk – Lens Opacities	
Evidence for linking the risk to the medicine	A study revealed cataract formation in dogs and rats treated with high doses of bexarotene. Study results from an open-label, multicenter, phase 2 and 3 study conducted in 58 patients with biopsy-proven stage IA through IIA cutaneous T-cell lymphoma, to determine the safety and efficacy of oral bexarotene revealed that in only 2 patients, a new lens opacity or possible subtle worsening of bilateral cataracts was noted. The incidence of lens opacities was sporadic and not related to dose or duration of treatment.[12]
Risk factors and risk groups	• Older age • Diabetes • Smoking
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.7 and 4.8 PL section 2 and 4 Prescription Only Medicine **Additional risk minimisation measures:** None

Important Potential Risk – Hypoglycaemia in patients taking anti-diabetic medications or insulin	
Evidence for linking the risk to the medicine	No cases of hypoglycemia associated with the use of bexarotene as monotherapy have been reported.[10]
Risk factors and risk groups	• Aging • Use of sulfonylureas, insulin therapy • Low glycated hemoglobin (HbA1c) values • Long duration of diabetes
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL section 2 Prescription Only Medicine **Additional risk minimisation measures:** None

II.C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bexarotene 75 mg soft capsules.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Bexarotene 75 mg soft capsules.